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Abstract: Erythropoietic protoporphyria (EPP) is a hereditary disorder caused by deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway. The majority of EPP patients present with a clinical symptom of painful phototoxicity. Liver damage, the most serious complication of EPP, occurs in <5% of the patients. This report describes a case of an EPP patient who complained of worsening cutaneous symptoms, nervousness, and insomnia. Laboratory tests showed highly increased protoporphyrin concentration in erythrocytes and elevated serum transaminases that are indicative of EPP-related liver damage. The subsequent finding of decreased serum thyroid-stimulating hormone (TSH) and increased free triiodothyronine (FT3) and free thyroxine (FT4) concentrations, as well antibodies against both thyroid peroxidase (TPO) and TSH receptors, led to the diagnosis of Graves' disease. The patient received 500MBq of radioiodine (I131). Three months after the radioactive iodine therapy, the thyroid volume was reduced to 30% of pretherapeutic volume. Although the patient was slightly hypothyroidic, his liver enzymes returned to normal, his erythrocytic protoporphyrin concentration dropped fivefold, and his skin symptoms improved dramatically. The coexistence of Graves' disease and EPP is a statistically rare event as, besides our patient, there was one additional case reported in the literature. Although the exact mechanism whereby Graves' disease interacts with EPP is yet to be explored, we recommend testing thyroid function in EPP patients with liver complication to exclude hyperthyroidism as a potential cause

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CASE REPORT

Exacerbation of erythropoietic protoporphyria by hyperthyroidism

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Abstract Erythropoietic protoporphyria (EPP) is a hereditary disorder caused by deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway. The majority of EPP patients present with a clinical symptom of painful phototoxicity. Liver damage, the most serious complication of EPP, occurs in <5% of the patients. This report describes a case of an EPP patient who complained of worsening cutaneous symptoms, nervousness, and insomnia. Laboratory tests showed highly increased protoporphyrin concentration in erythrocytes and elevated serum transaminases that are indicative of EPP-related liver damage. The subsequent finding of decreased serum thyroid-stimulating hormone (TSH) and increased free triiodothyronine (FT3) and free thyroxine (FT4) concentrations, as well antibodies against both thyroid peroxidase (TPO) and TSH receptors, led to the diagnosis of Graves' disease. The patient received 500 MBq of radioiodine (I^{131}). Three months after the radioactive iodine therapy, the thyroid volume was reduced to 30% of pretherapeutic volume. Although the patient was slightly hypothyroidic, his liver enzymes returned to normal, his erythrocytic protoporphyrin concentration dropped fivefold, and his skin symptoms improved dramatically. The coexistence of Graves' disease and EPP is a statistically rare event as, besides our patient, there was one additional case reported in the literature. Although the exact mechanism whereby Graves' disease interacts with EPP is yet to be explored, we recommend testing thyroid function in EPP patients with liver complication to exclude hyperthyroidism as a potential cause.

Abbreviations

EPP	Erythropoietic protoporphyria
XLDPP	X-linked dominant protoporphyria
FECH	Ferrochelatase
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
ULN	Upper limit of normal
RDW	Red cell distribution width
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
TSH	Thyroid stimulating hormone
TPO	Thyroperoxidase
FT3	Free triiodthyronine
FT4	Free thyroxine
PAS	Periodic acid-Schiff

Introduction

Erythropoietic protoporphyria (EPP) is a rare inherited disease of heme biosynthesis. The affected enzyme, ferrochelatase, is the ultimate enzyme of the heme biosynthetic pathway and catalyses the insertion of iron into protoporphyrin to form heme (Anderson et al. 2001). A clinically similar disease, X-linked dominant protoporphyria (XLDPP), is caused by activating mutations of aminolevulinate synthase 2, the first enzyme of the pathway (Whatley et al. 2008). In both disorders, accumulation of the substrate of

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ferrochelatase, protoporphyrin IX, leads to dermal phototoxicity, which mainly affects the face and back of the hands. Seven years after the first description of EPP by Magnus et al. in 1961, Barnes et al. (1968) reported a case of EPP-related terminal liver failure elicited by hepatic accumulation of protoporphyrin IX. The life-long risk of terminal liver failure is estimated to be between 1% and 4% (Holme et al 2006; Doss and Frank 1989). A dramatic increase in the erythrocytic protoporphyrin concentration, together with a decrease of fecal protoporphyrin elimination and an increase in the amount of urinary coproporphyrin I-isomer, is regarded as a sign of impending EPP liver disease (Gross et al. 1998). Alcohol overconsumption was the first identified risk factor for the development of EPP-related liver failure (Bonkovsky and Schned 1986). Later, genetic factors, including null-allele mutations in the ferrochelatase (*FECH*) gene, as well as hypermethylation of the nonmutated *FECH* allele, were added (Minder et al 2002; Onaga et al 2004). Limited data available so far indicates that patients with the variant *XLDPP* are at a higher risk of developing liver affection than those with the classic EPP.

We report here that hyperthyroidism, a treatable disease, caused exacerbation of the cutaneous symptoms, a massive increase in the level of erythrocytic protoporphyrin concentration, and signs of liver involvement in a patient with classic EPP.

Case report

The 40-year-old man complained of worsening skin phototoxicity during the previous 6 months when he visited our clinic in early 2006. He presented with the typical EPP skin lesion on the nose. In addition, he also suffered from anxiety and insomnia. The patient was severely affected by phototoxicity during early childhood. As an adult, he had learned to cope with the disease and was able to carry out his daily activities without much restraint until late 2005. The diagnosis of EPP was made 13 years earlier at the French Center for Porphyrias, Paris, France, on the basis of reduced ferrochelatase activity in peripheral blood mononuclear cells. No record was available on the blood protoporphyrin concentration at the time of diagnosis. However, his urinary porphyrin concentrations were reportedly normal. Skin histology at that time showed abnormalities typical for EPP, including periodic acid-Schiff (PAS) deposits around the capillaries. The erythrocytic protoporphyrin concentration at his initial visit to our clinic was increased to a level that we considered as potentially risky for developing EPP liver affection, i.e., >40 μmol/L red blood cell (RBC) count. Liver function was therefore evaluated. As shown in Table 1, serum alanine aminotransferase (ALAT) was nearly two times above the upper limit of normal (ULN), and serum aspartate aminotransferase (ASAT) was slight above the ULN. The patient reported no excess alcohol consumption.

The patient's *FECH* gene was subsequently sequenced, leading to the identification of a heterozygous mutation, *p.* W34X. This is a known mutation of the *FECH* gene first described by Gouya et al. (2004). The patient was also heterozygous for the intronic polymorphism IVS3-48c/t. This genetic constellation confirmed the diagnosis of classic EPP. Hematologic values were largely normal, except for a slight increase in the RBC distribution width (RDW) and decreases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), a frequent finding among EPP patients (Holme et al. 2007; Delaby et al. 2009; Wahlin 2010). At the patient's second visit to our clinic 3 months later, both his protoporphyrin concentration and liver enzyme values remained unchanged. However, the concentration of urinary porphyrins, in particular coproporphyrin isomer I, was increased, which was a sign of cholestasis.

Because of his complains of nervousness and insomnia, thyroid function tests were performed. The results showed a decrease in serum TSH and a concomitant increase of both FT3 and FT4 (Table 1). In addition, antibodies against both thyroperoxidase (TPO) and TSH receptor (TRAb) were detected. Radioiodine uptake was increased, and the uptake was diffusely distributed over the entire gland, as demonstrated by scintigraphy. (Table 1). A diagnosis of Graves' disease was therefore made. Radioactive iodine therapy was chosen over thyrostatic drugs taking into consideration that these drugs, as an adverse effect, may cause further damage to the patient's liver. He received 500 MBq of I^{131}, corresponding to an ablative thyroid dose of 200 *Gy*. Six weeks later, mild hypothyroidism developed. He was substituted with thyroxine. Three months after the radioactive iodine therapy, the patient remained slightly hypothyroidic, and the dosage of thyroxine was therefore increased. Also, his thyroid volume, as determined by sonography, was decreased to 30% of the pretherapeutic volume (8 vs. 27 ml; Table 1). At the same time, a fivefold drop in the concentration of erythrocytic protoporphyrin was measured. Concomitantly, urinary porphyrin concentration and liver enzymes all returned to normal. Meanwhile, the patient noticed a dramatic improvement in his skin condition, i.e., the cutaneous phototoxicity was reduced to the degree he was accustomed to.

Discussion

Graves' disease is a relatively common disorder that occurs at any age but is especially common in the third and fourth decades of life. It can be found in approximately 1% of the population, or 1:89 individuals (Hollowell et al. 2002).

Table 1 Laboratory analyses of the Swiss and the Japanese patients

	The Swiss patient								The Japanese patient				
	Before treatment						After treatment		Before treatment	After treatment			
	1992	28 Mar 2006	07 June 2006	05 July 2006	17 July 2006	07 Aug 2006	26 Sep 2006	09 Nov 2006	25 Oct 1969	10 Nov 1969	11 Dec 1969	27 Jan 1970	20 Mar 1970
Free protoporphyrin in EC		**55.20** (<0.2 μmol/L)		**48.9**				**9.3**	585.3 (7-40 μg/dl)	125.4	151	161.7	148
Fecal protoporphyrin									175 (<100 μg/g dry weight)			21.3	
Urinary coproporphyrin I[a]				**16.0 (<8.4)**				3.5					
Urinary coproporphyrin III[a]				10.9 (<17.8)				7.6					
Ferrochelatase activity (units)	**1.2 (5±1.5)**												
Ferrochelatase genotype		**p.W34X**, IVS3-48c/t											
TSH (0.3-5.0)			**0.01**		**< 0.01**		**0.07**	**34.1**					
FT3 (3.1-7.2)			**17.2**		**28.8**		1.6	2.6	basic metabolic rate : +34%				
FT4 (11-26)			**40**		**50.9**		5.6	13.1	serum PBI: 22.0 ug/dl				
TRAb (<1)					**8.6**			**18.9**					
RAIU					24 h:75.6%; 48 h: 63.6%				4 h: 57%; 8 h: 64.2% and 24 h: 75.6%				
Thyroid volume (<25 ml)					27			8					
ASAT		**40 (<37)**				**42**		29	120 U				
ALAT		**75 (<41)**				**88**		33	78U				
Alkaline phosphatase		69 (<117)				82			14.5 KAU				
Red blood cells (mio/ul)									4.84				
Hemoglobin (g/dl)			14.1			14.9			11.6				
Erythrocyte half life									14 days				

Pathological values are in **bold**

EC erythrocyte,*FT3* Free triiodthyronine, *FT4* free thyroxine, *TRAb* thyroid-stimulating hormone receptor antibody, *RAIU* thyroid radioactive iodine uptake, *ASAT* aspartate aminotransferase, *ALT* alanine aminotransferase, *PBI* protein-bound iodine, *RDW* red blood cell distribution width, *KAU neg* king armstrong unit negative

[a] nmol/mmol creatinine

However, the chance for coexistence of Graves' disease and EPP is very low, i.e., 1:13 million individuals, since EPP is a relatively rare inborn disorder with an estimated prevalence of about 1:150,000 individuals (Schneider-Yin et al. 2009). The scarcity is evidenced by the fact that so far, only one additional case of EPP combined with Graves' disease has been reported in the literature, which was in 1969 (Yamada et al. 1971). In that report, the 16-year-old Japanese patient presented with a clinical course very similar to that of our patient, i.e., aggravation of EPP symptoms and signs of protoporphyrin-induced liver disease at the time when Graves' disease was diagnosed. The symptoms included dark skin rashes, signs of hyperthyroidism, jaundice, abnormal liver function, and a massive increase in erythrocytic protoporphyrin concentration (Table 1). As in our patient, the conditions in the Japanese patient improved dramatically after successful treatment of hyperthyroidism, i.e., normal liver function was restored and erythrocytic protoporphyrin concentration diminished (Yamada et al. 1971). The occurrence of Graves' disease in EPP, although very rare, caused an exacerbation of skin symptoms and more importantly, deterioration in liver function, in both patients, so that they were at risk of developing liver disease, the most serious and potentially life-threatening complication of EPP.

Interaction between hyperthyroidism and EPP is theoretically possible, as both diseases affect the liver and bone marrow. In EPP, bone marrow is the main source of protoporphyrin overproduction during erythropoiesis, whereas the liver/biliary tract is the only excretory route for excess protoporphyrin due to its hydrophobic nature. EPP patients present frequently with normo- to microcytic anemia due to disturbance in iron metabolism or iron distribution in the body (Lyoumi et al 2007; Holme et al 2007) or to a decreased rate of heme synthesis as the result of deficient ferrochelatase activity.

Mild liver dysfunction featured by elevated liver enzymes occurs frequently in hyperthyroid patients, whereas icterus can be observed in severe thyrotoxicosis (Gurlek et al. 1997; Beaver and Pemberton 1933). Erythropoiesis on the other hand, is increased in hyperthyroidism in order to meet the demand of an increase in oxygen delivery to the peripheral tissues. The enhanced erythropoiesis is reflected by a hypercellular bone marrow, in particular, an increased number of erythrocyte precursors. In general, hyperthyroid patients show increases in both the total RBC mass and total blood volume. As a result, their hemoglobin concentration could remain normal. Additional signs of enhanced erythropoiesis, including increased hemoglobin synthesis, shortened plasma iron clearance time, and increased iron turnover and RBC radioiron incorporation, can be observed in some hyperthyroid patients (18). In other patients, however, there is evidence of ineffective erythropoiesis, as seen by reduced MCV and erythrocyte survival time (Ford and Carter 1988). Iron deficiency, which negatively affects erythropoiesis, is also frequently observed in hyperthyroidism.

Experimental evidence, which indicate a possible link between thyroid hormone and the heme biosynthesis, came from a study of Bauer et al. (1998). In that study, the thyroid hormone receptor α (c-ErbA/TRα) was shown to be involved in the terminal differentiation of erythroid progenitors, i.e., upon binding to its ligand T3, c-ErbA/TRα induced a switching from proliferation to differentiation in gc-ErbA erythroblasts. Among the enzymes involved in erythroid differentiation, aminolevulinic acid synthase (ALAS) is the initial and rate-limiting enzyme of heme biosynthesis. In a study by Zenke et al. (1990), the amount of ALAS transcript in v2-ErbA-expressing erythroblasts was markedly increased in response to T3.

In both protoporphyrias—EPP and XLDPP—protoporphyrin IX accumulates in erythroblasts during the heme biosynthesis as the result of either a deficient ferrochelatase or an overactivity of ALAS-2 (the erythroid-specific ALAS). Based on the available information, it remains unclear whether hyperthyroidism causes exacerbation of EPP by increasing the rate of heme synthesis, by impairing liver excretory function for protoporphyrin, or by other unknown mechanisms. Therefore, we recommend testing thyroid function in protoporphyria patients with an accompanying liver malfunction in order to exclude hyperthyroidism as a potential cause.

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